Endocardial left ventricular pacing improves cardiac resynchronization therapy in chronic asynchronous infarction and heart failure models

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Abstract: BACKGROUND: Studies in canine hearts with acute left bundle branch block (LBBB) showed that endocardial left ventricular (LV) pacing improves the efficacy of cardiac resynchronization therapy (CRT) compared with conventional epicardial LV pacing. The present study explores the efficacy of endocardial CRT in more compromised hearts and the mechanisms of such beneficial effects. METHODS AND RESULTS: Measurements were performed in 22 dogs, 9 with acute LBBB, 7 with chronic LBBB combined with infarction (embolization; LBBB plus myocardial infarction, and concentric remodeling), and 6 with chronic LBBB and heart failure (rapid pacing, LBBB+HF, and eccentric remodeling). A head-to-head comparison was performed of the effects of endocardial and epicardial LV pacing at 8 sites. LV activation times were measured using 100 endocardial and epicardial electrodes and noncontact mapping. Pump function was assessed from right ventricular and LV pressures. Endocardial CRT resulted in better electric resynchronization than epicardial CRT in all models, although the benefit was larger in concentrically remodeled LBBB plus myocardial infarction than in eccentrically remodeled LBBB+HF hearts (19% versus 10%). In LBBB and LBBB+HF animals, endocardial conduction was 50% faster than epicardial conduction; in all models, transmural impulse conduction was 25% faster when pacing from the endocardium than from the epicardium. Hemodynamic effects were congruent with electric effects. CONCLUSIONS: Endocardial CRT improves electric synchrony of activation and LV pump function compared with conventional epicardial CRT in compromised canine LBBB hearts. This benefit can be explained by a shorter path length along the endocardium and by faster circumferential and transmural impulse conduction during endocardial LV pacing.

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Background—Studies in canine hearts with acute left bundle branch block (LBBB) showed that endocardial left ventricular (LV) pacing improves the efficacy of cardiac resynchronization therapy (CRT) compared with conventional epicardial LV pacing. The present study explores the efficacy of endocardial CRT in more compromised hearts and the mechanisms of such beneficial effects.

Methods and Results—Measurements were performed in 22 dogs, 9 with acute LBBB, 7 with chronic LBBB combined with infarction (embolization; LBBB plus myocardial infarction, and concentric remodeling), and 6 with chronic LBBB and heart failure (rapid pacing, LBBB+HF, and eccentric remodeling). A head-to-head comparison was performed of the effects of endocardial and epicardial LV pacing at 8 sites. LV activation times were measured using ≈100 endocardial and epicardial electrodes and noncontact mapping. Pump function was assessed from right ventricular and LV pressures. Endocardial CRT resulted in better electric resynchronization than epicardial CRT in all models, although the benefit was larger in concentrically remodeled LBBB plus myocardial infarction than in eccentrically remodeled LBBB+HF hearts (19% versus 10%). In LBBB and LBBB+HF animals, endocardial conduction was ≈50% faster than epicardial conduction; in all models, transmural impulse conduction was ≈25% faster when pacing from the endocardium than from the epicardium. Hemodynamic effects were congruent with electric effects.

Conclusions—Endocardial CRT improves electric synchrony of activation and LV pump function compared with conventional epicardial CRT in compromised canine LBBB hearts. This benefit can be explained by a shorter path length along the endocardium and by faster circumferential and transmural impulse conduction during endocardial LV pacing. **(*Circ Arrhythm Electrophysiol*. 2012;5:191-200.)**

Key Words: pacing ■ heart failure ■ cardiac resynchronization therapy ■ electrophysiology ■ bundle-branch block

Cardiac resynchronization therapy (CRT) is an established treatment for patients with moderate-to-severe heart failure (HF) and a wide QRS complex.[1] However, the amount of reverse remodeling and clinical improvement is highly variable and a considerable amount of patients respond poorly to the therapy.[1]

Clinical Perspective on p 200

In conventional CRT, the left ventricular (LV) lead is transvenously positioned in a coronary vein, which results in epicardial (EPI) LV pacing. As a consequence, the initiated electric wave front propagates over the epicardium and through the LV wall toward the endocardium. Under physiological conditions, electric activation of the LV initiates at the endocardium.[2] Endocardial (ENDO) LV pacing results in less asynchronous activation of the LV free wall than EPI LV pacing.[3] In dogs with acute left bundle branch block (LBBB), ENDO LV pacing during CRT (ENDO-CRT) has increased the benefits of CRT.[4] Compared with EPI-CRT, ENDO-CRT improved LV systolic pump function in combination with better electric resynchronization and less dispersion of repolarization.

Three possible mechanisms explaining the more rapid electric activation during ENDO-CRT were proposed: (1) shorter path length of conduction, (2) faster endocardial than epicardial conduction, and (3) faster conduction from endocardium to epicardium than vice versa. Although all 3 factors may contribute in the setting of acute LBBB in otherwise healthy canine hearts, several factors may potentially diminish the benefit of ENDO-CRT in patients. First, the influence

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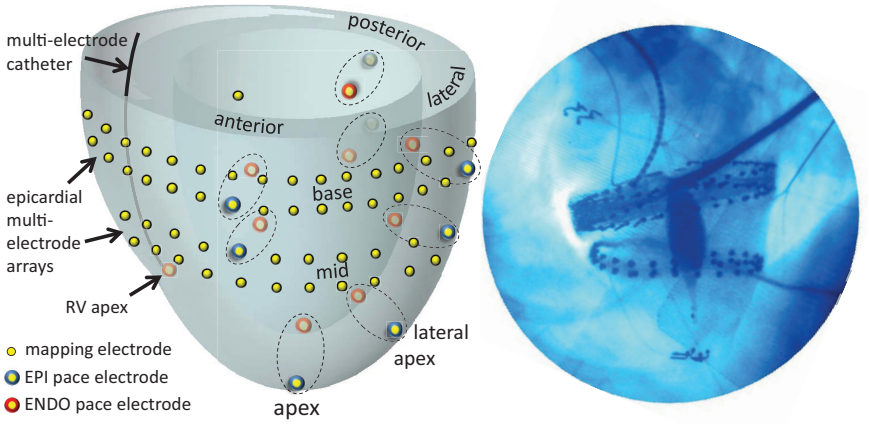

Figure 1. Schematic setup of the experiment (left panel) with mapping electrodes depicted as yellow dots. The 8 pacing electrodes have an additional blue (EPI) or red (ENDO) border. The fluoroscopic image (right panel) shows the mapping electrodes and multielectrode array in place.

of an infarct on impulse conduction in asynchronous hearts is not understood and may differ between myocardial layers.[4] Second, ventricular dilatation and wall thinning would reduce the difference in conduction path length between endocardium and epicardium, potentially reducing the advantage of ENDO-CRT in patients with dilated cardiomyopathy. In addition, Spragg et al showed that, in canine hearts with chronic LBBB, impulse conduction was reduced, especially in the endocardium of the late activated regions, exactly the region where an ENDO LV pacing lead could be positioned.[5] A better understanding of the various factors determining the benefits of ENDO-CRT in animal models with compromised hearts is warranted to better understand the ambivalent results reported from the few small clinical studies on endocardial CRT.[6–9]

To this purpose, we investigated the efficacy of ENDO-CRT in 3 animal models: canine hearts with acute LBBB and chronic LBBB in combination with myocardial infarction (LBBB+MI, induced by coronary embolization) or with dilated cardiomyopathy (LBBB+HF, induced by rapid pacing). To better understand the mechanisms of ENDO-CRT, we also performed more detailed electrophysiological measurements compared with our earlier studies in acute LBBB.[4]

Methods

Animal handling was performed according to the Dutch Law on Animal Experimentation and the European Directive for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (86/609/EU). The protocol was approved by the Experimental Animal Committee of Maastricht University.

Experimental Models

Twenty-two adult mongrel dogs of either sex and unknown age, weighing 29.5±2.0 kg, were divided into 3 groups: acute LBBB (n=9, of which some data were already previously reported[4]), LBBB+MI (n=7), and LBBB+HF (n=6). Animals were induced by intravenous pentothal administration and anesthetized by continuous infusion of midazolam (0.25 mg/kg per hour IV) and sufentanil (3 μg/kg per hour IV).

In the LBBB+MI group, transmural infarction was created by embolization of the left circumflex (n=3) and left anterior descending (n=4) arteries using a suspension of ≈1 mL dry volume polyvinyl alcohol foam particles; 4 weeks later, LBBB was induced.[10] Infarct size (% LV mass) and transmurality were determined by triphenyltetrazolium chloride staining postmortem.[10] In the LBBB+HF group, LBBB was created and, during the same procedure, a standard pacing lead was placed in the apex of the right ventricle (RV) and connected to a pacemaker (Medtronic InSync III). After a week of recovery, the heart was paced at a rate of 220 beats per minute for 4 weeks to induce systolic LV dysfunction, as described by other groups.[11,12] In both models, M-mode recordings of 2D echocardiography measurements from the midventricular papillary muscle level were obtained at baseline and just before the final measurements.

CRT Studies

Five weeks after creating the infarction (LBBB+MI) or 4 weeks after turning on the pacemaker (LBBB+HF), the animals were anesthetized again, as previously described, for the acute CRT studies. RV and LV pressure catheters were positioned as reported earlier.[4] After opening the chest, 2 multielectrode arrays holding 102 contact electrodes were placed around the heart, which measured epicardial electric potentials (Figure 1). Additional EPI LV electrodes were placed at the apex and lateral apex. An octapolar electrode catheter (Daig Livewire TC; Minnetonka, MN) was positioned against the RV-septum. Eight LV EPI electrodes were selected for pacing at various wall regions: anterior base, lateral base, posterior base, midanterior, midlateral, midposterior, lateral apex, and apex. For a paired comparison between EPI and ENDO LV pacing, custom-made plunge electrodes were inserted at these exact sites to enable ENDO-CRT and endocardial LV mapping (Figure 1).

Pacing Protocol

All pacing was performed in D00 mode, using atrial pacing at ≈10 beats per minute higher than the intrinsic rate. Between each switch of LV pacing site (8 EPI and 8 ENDO), baseline atrial pacing measurements were made during 3 respiratory cycles. During biventricular pacing, the RV apex was stimulated simultaneously with the selected EPI or ENDO LV electrode, using the longest atrioventricular interval that ensured complete biventricular capture.

After hemodynamic measurements in the LBBB and LBBB+HF dogs, a noncontact multielectrode array (EnSite 3000, Figure 1) was introduced into the LV to enable localization of the LV endocardium and plunge electrodes.[13] Subsequently, the pacing protocol was repeated while deriving 2048 virtual electrograms around the endocardial LV simultaneously and storing them for off-line analysis.

Data Analysis

From the surface ECG, QRS width and time from T-peak to T-end were determined.[4] For all electrodes, depolarization times were calculated as the time difference between the onset of the Q-wave (during baseline) or ventricular pacing artifact (during CRT) and the time of steepest deflection in the electrogram ($-dV/dt_{max}$). 3D

depolarization time maps were created by plotting the depolarization times on epicardial and endocardial models using custom MATLAB software (MathWorks; Natick, MA).[14] *Activation times* (ATs) were defined as the maximum depolarization time difference and were calculated for specific LV layers (endocardium, epicardium, and transmural) and for the total LV. LV EPI electrodes were considered to be the band electrodes on the LV wall, the LV apical plunge electrodes, and the RV septal electrodes.

Because endocardial LV AT was derived from a small amount of plunge electrodes, the 2048 virtual electrograms, as derived from the multielectrode array (EnSite 3000), were used to calculate endocardial LV AT in an alternative way to compare with the plunge electrode measurements. Conduction velocities were calculated in the acute LBBB and LBBB+HF groups for anterior, lateral, and posterior regions between the paced electrode and their neighboring electrodes in the same myocardial layer by dividing the interelectrode distance by the difference in AT. For epicardial conduction velocity, this distance was equal to the interelectrode distance on the epicardial bands. For the endocardial conduction velocity, the endocardial interelectrode distance was derived from the shortest path length between these electrodes over the endocardial contour, as calculated by the EnSite system. Hemodynamic data analysis was performed as previously described.[4]

Statistical Analysis

Continuous data are presented as mean±SD and discrete variables as counts and percentage. A series of general linear regression models were used to compare pacing sites and experimental models for the several end points, with identity or logistic link function according to the dependent variable assessed. To account for intraindividual correlation of measurements (panel data), Huber-white robust SEs were calculated. No missing data imputation was performed. Stata 10 (StataCorp; College Station, TX) was used for computation. A 2-sided $P<0.05$ was considered statistically significant. Bonferroni correction was used for post hoc comparisons.

Results

In all 22 experiments, 8 EPI-ENDO pairs of LV pacing sites were evaluated during biventricular pacing. Because of occasional misplacement of the endocardial electrode or unstable hemodynamic conditions, 151 of the possible 176 paired data sets were successfully acquired.

Experimental Models

Table 1 summarizes the baseline characteristics of hearts with acute LBBB, LBBB+MI, and LBBB+HF during the CRT protocol. All infarctions were transmural, and infarct size accounted for 20±16% (range, 14%–32%) of LV mass. Compared with the acute LBBB group, LV function was depressed in the LBBB+MI group, as indicated by lower stroke work and elevated LV and RV end-diastolic pressures. Echocardiographically, LV end-diastolic diameter remained constant while wall thickness increased (Table 1). Consequently, the ratio of outer/inner LV radius was higher in the LBBB+MI group compared with the acute LBBB group (1.88 versus 1.61, respectively; general linear model [post hoc comparison] $P<0.05$), indicating concentric remodeling. In the LBBB+HF group, 4 weeks of rapid pacing induced an increase in LV end-diastolic diameter and a decrease in LV wall thickness. In this model, the ratio of outer/inner LV radius was decreased to 1.36 (general linear model [post hoc comparison] $P<0.05$), reflecting eccentric remodeling, which was accompanied by severe systolic dysfunction, as evidenced by an LV ejection fraction of ≈15% in combination with ≈50% reduction of LV dP/dt_{max} and elevated LV EDP (Table 1).

Table 1. Baseline Electrocardiography, Echocardiography, and Hemodynamic Characteristics of the LBBB, LBBB+MI, and LBBB+HF Groups

Characteristics	LBBB (n=9)	LBBB+MI (n=7)	LBBB+HF (n=6)
Electrocardiographic parameters			
Heart rate, bpm	117±11	125±16	135±10*
QRS width, ms	116±8	106±9	123±10
Echocardiographic parameters			
LV end-diastolic diameter, cm	3.97±0.45	4.09±0.37	4.90±0.36*
LV posterior wall thickness, cm	1.14±0.18	1.41±0.12*	0.90±0.11*
LV septum wall thickness, cm	1.31±0.09	1.53±0.16*	0.86±0.12*
LV ejection fraction, %	54±8	53±9	15±2*
Hemodynamic parameters			
LV dP/dt_{max}, mm Hg/s	1554±249	1409±282	842±82*
LV $-dP/dt_{min}$, mm Hg/s	1383±266	1495±344	976±175*
LV PSP, mm Hg	91±11	87±13	76±10*
LV EDP, mm Hg	6±3	13±9*	18±11*
SV, mL	32±8	26±7	15±5*
SW, mm Hg/mL	1700±94	1208±593*	1044±434*
RV dP/dt_{max}, mm Hg/s	512±82	489±129	426±125
RV dP/dt_{min}, mm Hg/s	−264±36	−279±75	−388±165*
RV PSP, mm Hg	24±9	30±5	30±10
RV EDP, mm Hg	0±7	9±4*	8±5*
Mech.InterV.Asynch., ms	−27±7	−22±7	−23±11

Data are given as mean±SD.

EDP, end-diastolic pressure; Mech.InterV.Asynch., mechanical interventricular asynchrony; PSP, peak systolic pressure; SV, stroke volume; SW, stroke work.

*$P<0.05$ vs the LBBB group, using a general linear model for repeated measures and Bonferroni correction for post hoc comparisons.

Effects of ENDO-CRT on Impulse Conduction

Typical examples of electric activation in the ventricles for all 3 groups are shown in Figure 2. During baseline LBBB (left panels), the electric wave front initiated at the RV endocardium and gradually spread through the interventricular septum toward the latest activated LV lateral wall was consistent with electric maps from an earlier high-resolution mapping study.[15] During conventional EPI-CRT, activation wave fronts (red-yellow) generated in the RV and LV merged near the septum and anterior wall (green), thus resynchronizing the ventricles compared with baseline LBBB. ENDO-CRT (right panels) resulted in more pronounced resynchronization than EPI-CRT, as depicted by the more homogeneous color pattern (lack of green color) and less crowding of isochrone lines.

These mapping studies revealed that, in all models, ENDO-CRT significantly reduced total LV AT compared with

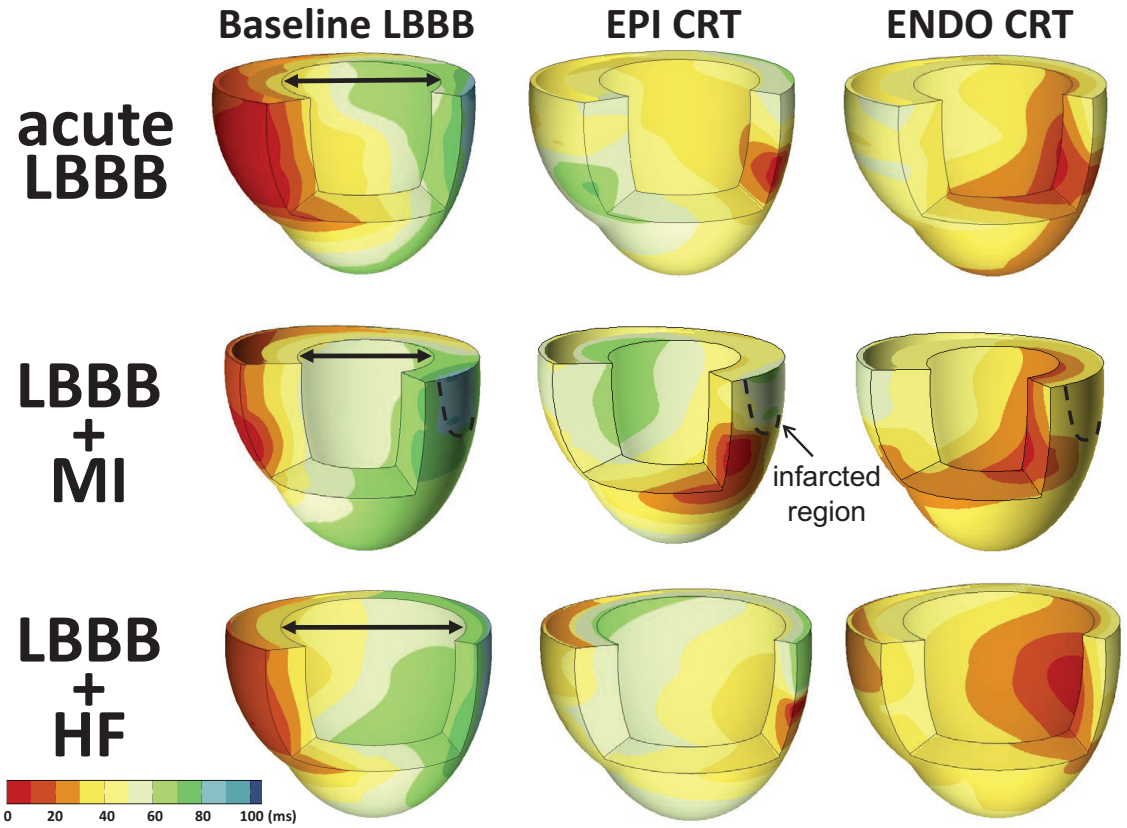

Figure 2. Typical examples of 3D electric activation in the LBBB, LBBB+MI, and LBBB+HF groups during baseline LBBB (left panels), CRT with EPI LV pacing (middle panels), and ENDO LV pacing (right panels). In both modes of CRT, the LV pacing lead was positioned at the midlevel of the LV wall. The size of the cavity and the wall thickness correspond approximately with the echocardiographic measurements.

EPI-CRT, which was associated with reduced QRS duration (Figure 3, Tables 2 and 3). The shorter total LV AT during ENDO-CRT was caused by shorter epicardial LV AT and shorter transmural LV AT. The latter is depicted in Figure 3 by the dashed arrow lines as the time to the first endocardial activation during EPI-CRT and the time to first epicardial activation during ENDO-CRT. A detailed indication of the spread of activation in the short axis is provided by Figure 4. Figure 4 also explains why endocardial LV AT was paradoxically increased by ENDO-CRT compared with EPI-CRT in Figure 3. During EPI-CRT, a broad wave front slowly approached the endocardium but caused almost simultaneous activation of a large part of the LV endocardium, whereas during ENDO-CRT, the earliest endocardial activation occurred in a small region that took time to spread to more remote areas of the LV endocardium. The endocardial LV AT, as derived from the LV contact electrodes, corresponded closely with those derived from multielectrode array mapping (plot in Figure 4), albeit that the plunge electrodes underestimated endocardial LV AT at higher values, presumably because the multielectrode array is more likely to include small late-activated regions.

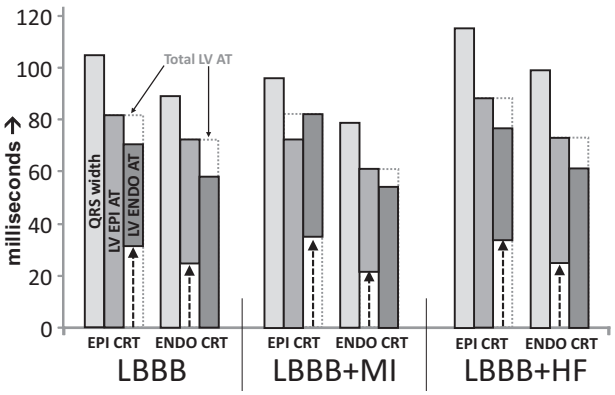

Figure 3. Overview of mean QRS duration, epicardial LV AT (activation time), and endocardial LV AT during EPI versus ENDO-CRT in dogs with LBBB, LBBB+MI, and LBBB+HF. Dashed bars indicate total LV AT; dashed arrows, transmural LV AT. All EPI-ENDO comparisons are statistically significant ($P<0.01$). Tables 2 and 3 provides absolute values and P values (all P values are based on the general linear model for repeated measures).

Comparing all measurements with baseline LBBB, ENDO-CRT reduced total LV AT significantly more than EPI-CRT in all 3 models (bottom panel of Figure 5, Tables 2 and 3). The improved resynchronization during ENDO-CRT was associated with ≈50% higher circumferential conduction velocities at the endocardium than at the epicardium (Figure 6A). This difference was consistent for all LV segments and was observed in hearts with acute LBBB and in LBBB+HF hearts. The added benefit of ENDO-CRT to resynchronize was larger in concentrically remodeled hearts (LBBB+MI) and least (19% versus 10%, respectively) in eccentrically remodeled hearts (LBBB+HF, Figure 6B), indicating that the

Table 2. Electrophysiological and Hemodynamic Variables During Baseline LBBB Conduction and During Epicardial and Endocardial CRT in Dogs With LBBB and MI

Variables	Baseline LBBB+MI	EPI-CRT	ENDO-CRT	*P* Value (ΔEPI vs ΔENDO)
HR, bpm	125±16	124±17	124±18	0.486
QRS width, ms	106±9	96±17*	79±12*	<0.001
Total LV AT, ms	88±7	81±16*	66±12*	<0.001
Epicardial LV AT, ms	88±7	81±16*	40±11*	<0.001
Endocardial LV AT, ms	52±16	47±15	54±10	0.003
Transmural AT, ms	…	36±21	21±11	<0.001
T_{peak}-T_{end}, ms	63±4	52±12	49±11	0.358
τ Value, ms	43±6	45±5	45±5	0.017
LV P_{max}, mm Hg	87±12	88±12	88±13	0.183
LV dP/dt_{max}, mm Hg/s	1410±282	1527±320*	1673±382*	0.005
LV dP/dt_{min}, mm Hg/s	−1495±344	−1550±340	−1551±375	0.711
LV EDP, mm Hg	13±7	14±8	14±7	0.362
SV, mL	20±7	21±8	21±8	0.384
SW, mm Hg*mL	1208±594	1403±692*	1586±775*	0.074
RV PSP, mm Hg	30±5	28±4	26±4	0.011
RV dP/dt_{max}, mm Hg/s	490±129	531±148	517±139	0.066
RV dP/dt_{min}, mm Hg/s	−280±75	−272±69	−288±90	0.351
RV EDP, mm Hg	9±4	10±4	9±3	0.408
Mech.InterV.Asynch., ms	−22±7	−16±9	−9±10	0.052

Data are given as mean±SD. In the last column, *P* values are presented for the differences in relative change (Δ) by EPI-CRT vs ENDO-CRT. All *P* values are based on the general linear model for repeated measures. Corresponding data for the acute LBBB group have been previously published.[4] Data are from 51 paired measurements in 7 experiments.

BiV, biventricular; bpm, beats per minute; EDP, end-diastolic pressure; Mech.InterV.Asynch., mechanical interventricular asynchrony; SV, stroke volume; SW, stroke work; PSP, peak systolic pressure.

*$P<0.05$ vs baseline LBBB.

smaller path length along the endocardium partly explains the benefit of endocardial CRT on electric resynchronization.

Effects of ENDO-CRT on Hemodynamic Performance

The superior electric resynchronization by ENDO-CRT coincided with larger increases in LV dP/dt_{max} than during EPI-CRT, and the absolute increase was similar for the 3 models (≈10% on top of the EPI-CRT effect, upper panel in Figure 5). A larger LV contractility improvement during ENDO-CRT was consistent for all paced regions and groups (with the exception of apicolateral pacing in the LBBB+HF group, Figure 7). Defining ≥10% increase in LV dP/dt_{max} as acute hemodynamic response to CRT, ENDO-CRT resulted in a hemodynamic response in 90% of cases, whereas EPI-CRT only resulted in a 59% response rate. Generally, the optimal sites during ENDO-CRT were located at the same wall regions as the optimal sites during EPI-CRT (Figure 8). However, endocardial sites providing a significant effect encompassed a larger LV area and magnitude of improvement was larger than for epicardial sites, as indicated by the more intense red colors. In LBBB hearts with LAD infarction, the best pacing sites were the basolateral LV wall, whereas in LBBB hearts with LCX infarction, LV midlateral to apicolateral wall sites provided the best results. In the acute LBBB and LBBB+HF groups, lateral and apicolateral pacing sites tended to perform better than anterior and posterior sites, but there was not an identifiable "optimal" ENDO or EPI pacing site (Figure 8). ENDO-CRT tended to increase stroke work compared with EPI-CRT; in the LBBB+HF group, ENDO-CRT also resulted in larger decreases in LV dP/dt_{min} than EPI-CRT (Table 3).

Discussion

The present study shows that endocardial CRT produces more uniform ventricular depolarization and larger hemodynamic benefit compared with conventional epicardial CRT in 3 models of experimental dyssynchrony: acute LBBB and chronic LBBB in combination with HF and with MI. The advantage of endocardial over epicardial CRT can, to a large extent, be understood from higher endocardial impulse conduction velocities, shorter transmural activation times, and shorter conduction path length, the latter explaining the less pronounced resynchronization in eccentrically remodeled LBBB+HF.

Mechanisms of Better Electric Resynchronization by LV Endocardial Pacing

From the data of our previous study[4] in canine hearts with acute LBBB, we suggested that the electric benefits of endocardial CRT could be explained by 3 factors: (1) a shorter path length for the depolarization wave to reach all

Table 3. Electrophysiological and Hemodynamic Variables During Baseline LBBB Conduction and During Epicardial and Endocardial CRT in Dogs With LBBB and Dilated Cardiomyopathy

Variables	Baseline LBBB+HF	EPI-CRT	ENDO-CRT	*P* Value (ΔEPI vs ΔENDO)
HR, bpm	135±10	135±9	135±9	0.175
QRS width, ms	123±10	116±16	99±20*	0.005
Total LV AT, ms	97±16	87±13*	76±17*	<0.001
Epicardial LV AT, ms	97±16	85±12*	49±16*	<0.001
Endocardial LV AT, ms	37±10	42±11	61±13*	<0.001
Transmural AT, ms	…	35±11	26±9	0.002
T_{peak}-T_{end}, ms	56±8	44±13*	45±18*	0.883
τ Value, ms	57±20	49±22	46±21	0.297
LV P_{max}, mm Hg	76±10	78±9	78±10	0.87
LV dP/dt_{max}, mm Hg/s	842±82	1009±153*	1090±221*	0.106
LV $dP/dt_{max}/P_{normed}$, mm Hg/s	22.3±5	26.9±7*	29±7*	0.002
LV dP/dtmin, mm Hg/s	−976±175	−1091±241*	−1177±281*	0.039
LV EDP, mm Hg	18.3±11	18.3±14	17.7±15	0.386
SV, mL	15±5	20±9*	20±10	0.556
SW, mm Hg*mL	1088±398	1363±644*	1467±767*	0.170
RV PSP, mm Hg	30±10	28±9*	28±9*	0.640
RV dP/dt_{max}, mm Hg/s	426±125	442±102	437±142	0.823
RV dP/dt_{min}, mm Hg/s	−388±165	−384±172	−412±176	0.001
RV EDP, mm Hg	8±5	8±7	8±7	0.662
Mech.InterV.Asynch., ms	−23±11	−16±9	−9±10*	0.008

Data are given as mean±SD. In the last column, *P* values are presented for the differences in relative change (Δ) by EPI-CRT vs ENDO-CRT. All *P* values are based on the general linear model for repeated measures. Data are from 48 paired measurements in 6 experiments.

bpm, beats per minute; EDP, end-diastolic pressure; Mech.InterV.Asynch., mechanical interventricular asynchrony; SV, stroke volume; SW, stroke work; PSP, peak systolic pressure.

*$P<0.05$ vs baseline LBBB.

regions of the ventricles, (2) more rapid impulse conduction in the endocardium than in the epicardium, and (3) a more rapid transmural conduction from endocardium to epicardium than in the opposite direction.[4] The present study extends these observations and provides more robust and more detailed evidence for these mechanisms.

Although obviously the path for impulse conduction is always shorter along the endocardium than along the epicardium, the difference depends on the eccentricity of ventricular remodeling. The finding that the added benefit of endocardial over epicardial CRT on electric resynchronization was greater in hearts with concentric than with eccentric remodeling supports the idea of a role for the shorter path length in the benefits of endocardial CRT. However, even in the most eccentrically remodeled hearts, a clear benefit remained, indicating important roles for other factors.

The most predominant factor with respect to the added benefit of endocardial pacing appears to be the faster impulse conduction in the endocardial layers. This fast conduction was even observed in the chronically dyssynchronous failing hearts and without regional differences. These results seem to contradict results from in vitro mapping studies by Spragg et al, who showed endocardial conduction slowing in lateral regions of chronically dyssynchronous canine hearts.[5] These contradictory findings might be explained by the difference in setup (perfused versus in vivo wedge preparations). Factors such as hypoxia, tissue damage during isolation of the wedge, and perfusion with crystalline medium may have influenced the in vitro measurements. On the other hand, distance along the endocardium may have been assessed less accurately in our in vivo preparation. Finally, Spragg et al measured along the main axis of a diagonally propagating wave front, whereas we selectively measured velocity in a circumferential direction.

In addition to a faster endocardial than epicardial impulse conduction, we also consistently found that impulse conduction across the LV wall was ≈25% faster when pacing the LV endocardium than when pacing the LV epicardium, thus adding to the more rapid total LV resynchronization. This difference in transmural conduction velocity is not well understood, because it would be expected that the conduction path is the same. Interestingly, this effect was observed even in the LBBB+HF group, even though LV wall thickness was decreased by ≈21%, thus contributing to the better electric resynchronization during endocardial CRT.

Comparison With Clinical Studies

LV endocardial pacing in humans can be established through an atrial transseptal approach.[6–8] The results of our study are,

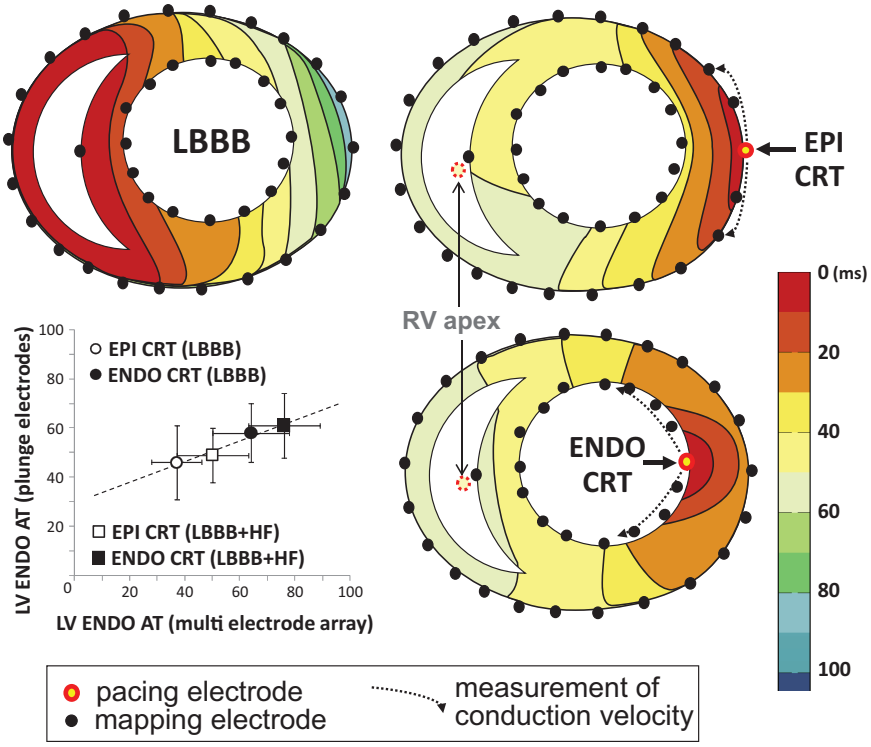

Figure 4. Typical examples of short-axis electric activation during baseline LBBB (left), EPI-CRT (top right), and ENDO-CRT (bottom right), obtained by electrode band and multielectrode array mapping. Transmural and epicardial isochrone broadening during ENDO-CRT indicate faster depolarization, but the endocardium is depolarized later than during EPI-CRT, as indicated by the isochrone narrowing. Dotted lines indicate the electrodes from which activation times were derived and divided by their distance to the pacing electrode to obtain conduction velocity. The graph plot shows the correlation between ENDO AT derived by the plunge electrodes and by the multielectrode array during EPI and ENDO-CRT in the LBBB and LBBB+HF groups.

at least in part, supported by a few small observational studies in human CRT patients in whom such an approach has been followed. In these clinical studies, LV dP/dt_{max} at the best LV endocardial site was significantly greater than that with device pacing via the coronary sinus.[7–9] Recently, these findings were debated to be subjected to statistical bias because the best LV ENDO site was selected among many (≤51) LV endocardial sites, which were compared with a single LV EPI site (via the coronary sinus).[16] By using this method, a relatively small measurement error could project into a rather wide range of extreme results.[16] In contrast, in our study, we used 8 sites, evenly spread over the LV free wall, and back-to-back comparison of endocardial and epicardial CRT, thus eliminating these site-specific biological pacing effects and statistical bias. In the clinical studies that compared the effect of pacing the coronary sinus electrode with the corresponding, immediately opposite, LV endocardium, the statistical significance was lost, but the trend still was toward a better effect of endocardial CRT.[7,8] A possible explanation for the lack of statistical significance in the clinical studies may be the fact that 1 study only investigated single-site LV pacing,[7] which, in the present canine study, also did not result in significant LV dP/dt_{max} differences when using short atrioventricular intervals (data not shown). In another study,[8] the direct comparison could only be made in 7 patients, resulting in low statistical power. An additional advantage of our animal experiment may have been the higher accuracy of positioning the pacing leads at directly opposite sides of the LV wall because of the direct access to the heart. Clearly, a more systematic study is required to certify the benefit of endocardial over epicardial CRT in patients.

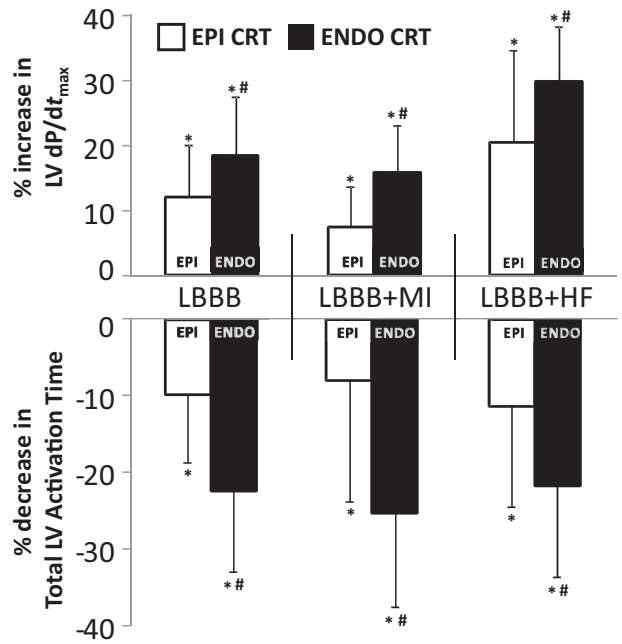

Figure 5. Percentage change in LV dP/dt_{max} (top panel) and during LV total activation duration (bottom panel) during EPI versus ENDO-CRT in dogs with LBBB, LBBB+MI, and LBBB+HF. *$P<0.05$ compared with baseline atrial pacing. #$P<0.05$ compared with EPI-CRT. (All P values are based on the general linear model for repeated measures.)

Most clinical studies used either QRS duration or solely epicardial or endocardial activation time to assess electric asynchrony, whereas few studies measured total (epicardial and endocardial) activation time. As in our study, Ginks et al used multielectrode array (EnSite) measurements of endocardial LV AT and found no reduction in this variable when moving from epicardial to endocardial CRT.[9] This observa-

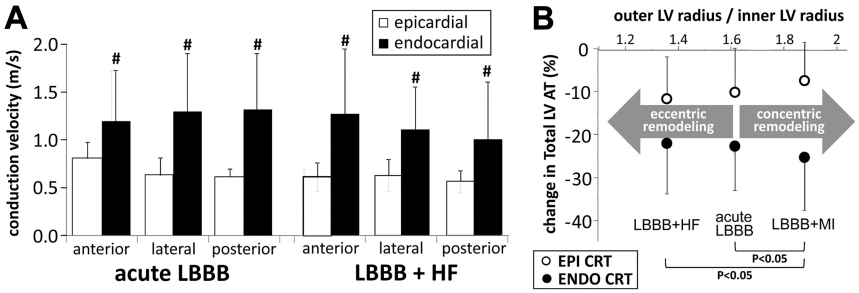

Figure 6. A, Mean±SD of conduction velocities (in m/s) of the epicardium and endocardium in anterior, lateral, and posterior regions in dogs with acute LBBB and chronic LBBB+HF. #$P<0.05$ for epicardial versus endocardial. **B**, Percentage change in total LV AT during EPI vs ENDO-CRT as a function of the ratio of outer/inner LV radius in the 3 experimental groups. *P* values signify a statistical difference in ENDO-EPI difference between groups. (All *P* values are based on the general linear model for repeated measures.)

tion was also made in our study, actually demonstrating an increase of endocardial LV AT on endocardial CRT. However, this paradoxical increase was inconsequential, because of the reduction in epicardial LV and transmural AT, such that total LV AT was reduced. Comparable to our results achieved in canine hearts, Ginks et al found that endocardial LV AT encompassed ≈40% of the QRS duration.[9] Therefore, endocardial conduction velocity is most likely similarly higher than epicardial conduction in patients, which is an important factor in the mechanism of endocardial CRT. The present study shows 1 possible reason why endocardial CRT may be less beneficial in patients with dilated HF. The smaller endocardial to epicardial path length difference in patients with dilated hearts could preclude the better resynchronization, but the hemodynamic benefits remain in favor of endocardial CRT, presumably because of the role of faster transmural and endocardial conduction.

In the latter respect, Ginks et al made an important observation, in that they observed smaller benefits at endocardial sites with slow conduction, possibly related to scar or hypoperfusion. This observation may seem in contradiction with our observation that the benefit of endocardial pacing was largest in the LBBB+MI group. However, in our study, we avoided pacing inside the infarcted area. In fact, MI does not preclude benefits of CRT, but the efficacy is more dependent on location and timing of stimulation, as has also been shown in a previous report.[10] In addition, a recent publication provides evidence that pacing in the scar strongly reduces the benefit of CRT.[17] Therefore, it is still plausible that ENDO-CRT can increase therapy response in ischemic patients. In this respect, an important benefit of endocardial CRT is that more pacing sites can be reached than usual with coronary venous implants. Exploring the sites appears important in light of the findings of Ginks et al and of our finding that there was no single optimal endocardial pacing site that showed consistently better hemodynamics. Helm et al investigated >100 pacing sites in failing and nonfailing asynchronous canine hearts and found, in agreement with our results, that average CRT response was excellent in a fairly broad range of the LV lateral wall. Thus, individual tailoring of endocardial CRT by searching the optimal pacing site within the endocardium is warranted. The fact that endocardial CRT provides consistently better electric resynchronization and hemodynamic improvement in the 3 different animal models further supports the idea that endocardial CRT is the ultimate preference in a wide variety of patients with dyssynchrony. This benefit may be enhanced by the larger range of accessible locations at the endocardium.

Endocardial CRT in Specific LBBB Models

Interestingly, despite all differences between the 3 models, CRT resulted in a similar absolute increase in LV dP/dt_{max} (all ≈150 mm Hg/s with EPI-CRT and ≈250 mm Hg/s with endocardial CRT). Because baseline LV dP/dt_{max} was considerably lower in the LBBB+HF group, this translated to higher relative increases in LV dP/dt_{max} during CRT, relative increases that are similar to those found in patients.[18] Interestingly, in CRT patients, a wide range of baseline LV dP/dt_{max} is observed, yet the increase in LV dP/dt_{max} on CRT is also ≈200 mm Hg/s. This indicates that there is an almost

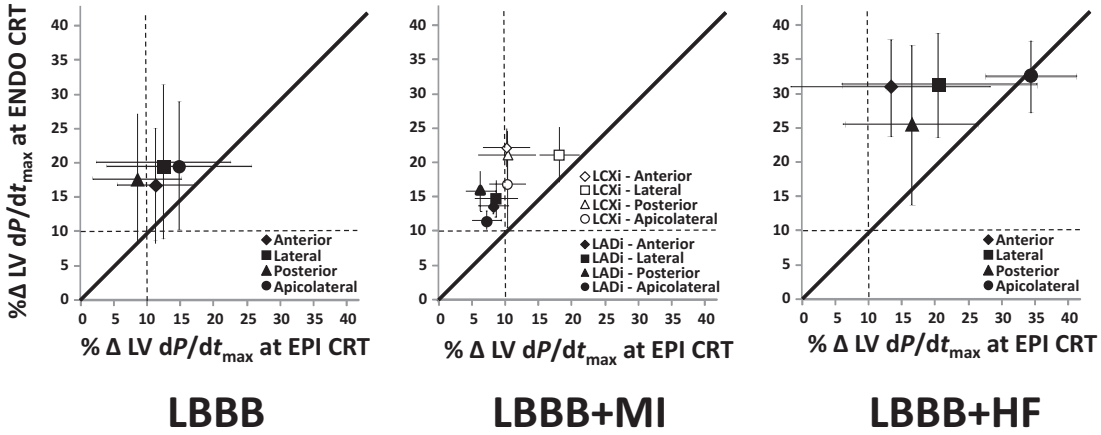

Figure 7. Increase in LV dP/dt_{max} (mean values and SD, pooled by regions, compared with baseline) during ENDO-CRT as a function of the percentage increase in LV dP/dt_{max} during EPI-CRT in dogs with LBBB, LBBB+MI, and LBBB+HF.

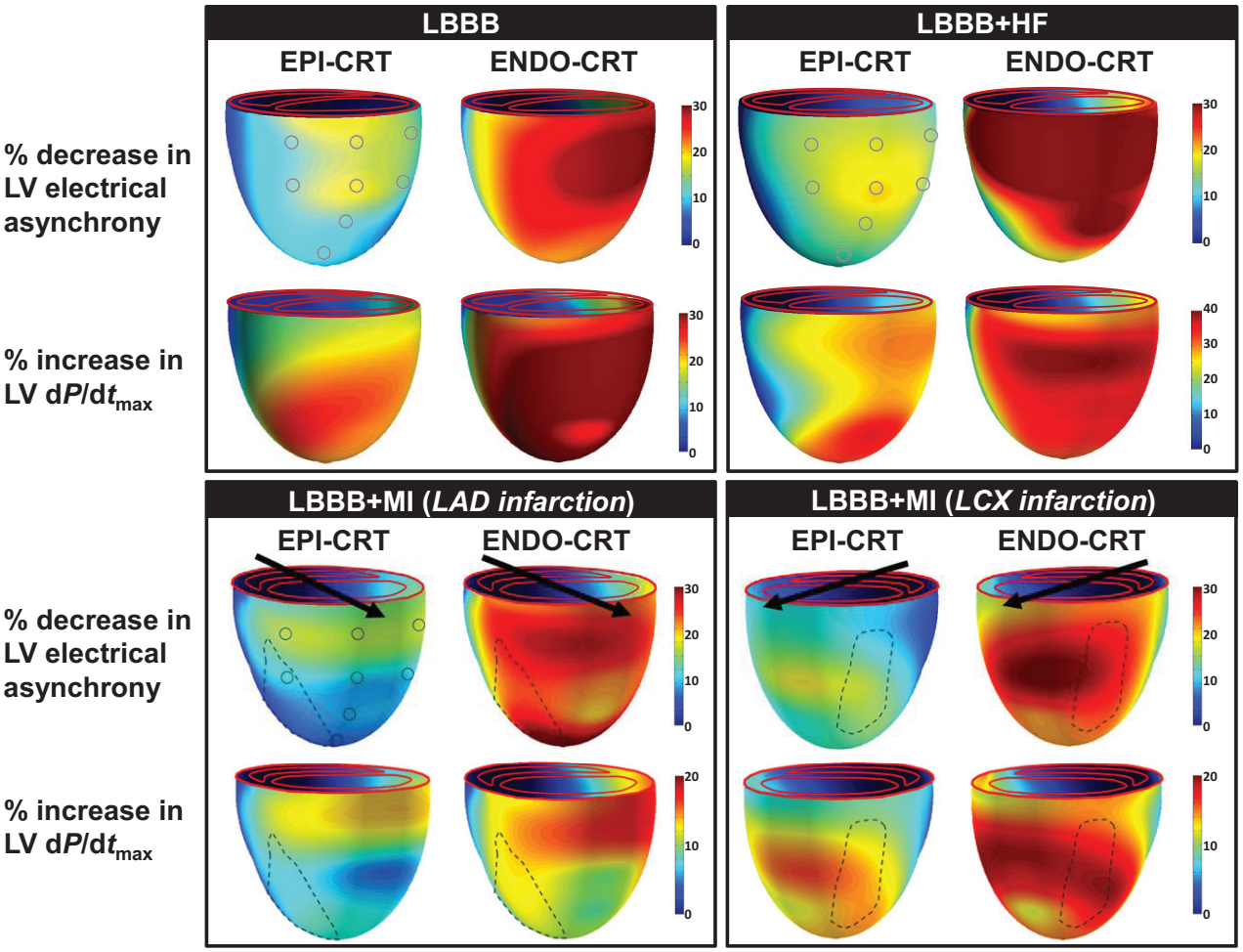

Figure 8. Spatial distribution of pacing sites (indicated by gray circles) that provide a certain percentage increase in LV electric resynchronization and LV dP/dt_{max} during EPI-CRT and ENDO-CRT compared with baseline atrial pacing. Plots are based on mean values from 6 LBBB hearts (top left panels), 6 LBBB+HF hearts (top right panels), 4 LBBB+MI hearts with LAD infarction (bottom left panels), and 3 LBBB+MI hearts with LCX infarction (bottom right panels). Dashed lines indicate region of infarction; arrows, rotation of LAD vs LCX. Impression of variation in measurements can be obtained from the error bars in Figure 7.

fixed increase in this parameter by CRT, which, as we show, can be increased by using a better (endocardial) pacing site.

Limitations

Although current chronic animal models resemble CRT candidates better than the acute LBBB model, our data should be extrapolated to patients with care. The LBBB+MI model has been introduced in a previous publication.[10] It is characterized by preserved LV ejection fraction, but elevated LV and RV filling pressures, and reduced stroke work. In this model, LBBB was induced by ablation of the proximal left bundle branch. Thus, the induced conduction abnormality may differ from that in patients with an ischemic cause of HF, in whom the ischemia may be the underlying cause of the conduction abnormality.

The LBBB+HF model has been used before by other groups. Even in these "chronic" animal models, the disease history is shorter than in patients; in addition, fibrosis and molecular remodeling may differ between animals and patients. Furthermore, the present study investigated the short-term hemodynamic response, whereas the long-term response, reverse remodeling, and survival are more relevant. Long-term follow-up of patients with endocardial CRT is limited to a small study, comparing 8 patients with endocardial CRT with 17 conventional (epicardial) CRT patients.[6] This study found more homogeneous intraventricular resynchronization, better LV filling, and increased systolic performance after 6 months. Clearly, larger long-term follow-up of endocardial CRT in patients is indicated.

Conclusions

In the canine model of chronic LBBB combined with MI or dilated cardiomyopathy, endocardial CRT improves electric synchrony of activation and LV function, compared with conventional epicardial CRT. The extent of additional electric resynchronization by endocardial CRT is dependent on cardiac remodeling, but the functional response is not. Therefore, this study further emphasizes the relevance of investigating the benefits of endocardial LV stimulation in CRT patients.

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CLINICAL PERSPECTIVE

Conventionally, cardiac resynchronization therapy (CRT) is applied using a left ventricular (LV) pacing electrode, positioned at the LV epicardium (either in an epicardial vein or surgically screwed into the myocardium). However, physiological electric activation originates in the endocardium and spreads toward the epicardium. In a previous study performed at our laboratory in a canine model of acute left bundle branch block, we showed that pacing at the LV endocardium rather than the LV epicardium provides more pronounced electric resynchronization and hemodynamic benefit. However, more recent clinical studies have shown inconclusive evidence of superiority of endocardial over epicardial CRT. The present study investigated endocardial CRT in chronic dyssynchronous canine models with myocardial infarction or heart failure. This study demonstrates that, in animal models, endocardial CRT results in better resynchronization, which is explained by higher impulse conduction velocities along the endocardium and from endocardium to epicardium compared with velocities along epicardium and from epicardium to endocardium, respectively. Also, the shorter conduction path length along the endocardium compared with the epicardium contributes to more synchronous activation during endocardial CRT, although this factor contributes less in dilated failing hearts. The hemodynamic effects were congruent with the electric effects. Practical application of endocardial CRT will depend on the availability of reliable techniques and tools to implant the LV lead into the LV endocardium. Possible options are a transatrial-septal approach, a longer screw electrode using a surgical approach, and the novel technique of leadless pacing.